Attorney Docket No. 9052-84

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Jurgen Denecke
Serial No.: 09/868,434
Filed: June 15, 2001

Group Art Unit: 1638
Examiner: A. Kubelik

For: *ENHANCING PLANT PATHOGEN RESISTANCE VIA INCREASING BIP LEVELS*

October 5, 2004

Commissioner for Patents
Post Office Box 1450
Alexandria, Virginia 22313-1450

DECLARATION UNDER 37 C.F.R § 1.132
OF JURGEN DENECKE, PhD.

Sir:

I, Jurgen Denecke PhD, do hereby declare and say as follows:

1. I received a Bachelor of Science degree (B.Sc) in Agricultural and Chemical Engineering from the University of Brussels, Belgium in 1986 and a Doctor of Philosophy degree (PhD.) from the University of Ghent in 1991. I am currently a Reader in the School of Biology at the University of Leeds, United Kingdom.

Additionally, I have delivered numerous lectures and authored and co-authored numerous articles and books in the areas of plant biotechnology, I am a named inventor for the present application and am knowledgeable of the contents of the above-identified patent application. I am also a co-author for the Crofts et al citation.

2. One of ordinary skill in the art of plant biochemistry would be apprised that at the time of filing the present application several non plant BiPs were in the public domain. For example BiPs had been identified in *Saccharomyces cerevisiae, Aspergillus*,

nematode worms, chicken, chinese hamsters and mice. BiPs were also known before December 1998 in *Arabidosis thaliana*, soybean, rice, maize, spinach and tobacco. (Please refer to Appendix I filed herewith for further details of BiPs in the public domain prior to December 1998). Therefore, the present application is adequately enabled for BiPs **other than** tobacco. Moreover, the high level of conservation was most rigorously demonstrated already in 1991 by my own experiments in which tobacco BiP was shown to functionally complement BiP in the yeast Saccharomyces cerevisiae. Tobacco BiP could fully replace the essential yeast BiP and sustain a viable strain (Denecke et al., 1991. The Plant Cell **3**, 1025-1035). One of ordinary skill in the art of plant biochemistry deduces from the high degree of conservation of BiP, even between kingdoms of organisms, that BiP from any eukaryotic cell, not just tobacco, would be sufficient to perform the invention. Indeed, even an artificially designed BiP which differs from any BiP in any given species would be appropriate so long as it possessed BiP **activity.**

I believe it would be possible for a competitor to develop plants and seeds from a plant over-expressing another BiP, for example a chicken BiP (see Appendix 1 example Stoeckle et al Mol. Cell. Biol. **8**, (7), 2675-2680, (1988)). This would bypass the present invention if it were limited to tobacco BiP. One of ordinary skill in the art of plant biochemistry would appreciate that a protein and its **activity** is what is crucial to the present invention **not** a nucleic acid sequence and a percentage of sequence identity.

Adequate definitions of "BiP Activity" are in the public domain and mainly illustrated in (Denecke et al., 1991. The Plant Cell **3**, 1025-1035) but also in (Leborgne-Castel et al., 1999. The Plant Cell **11**, 459-470). Indeed, the findings illustrated in Figure 12A on accelerated induction of PR1 (at 6 hours in BiP overproducers compared to 24 hours in wild type), or Figures 13 and 14 on the BiP-overexpression mediated resistance to the drug tunicamycin could also be used as routine methods of testing BiP **activity.**

Thus, in the present context, the specification supports the statement that the method of the present invention can be performed by over-expression of **any** BiP, not just plant BiPs and certainly not just BLP4.

3. I am a co-author of Crofts et al 1998, The Plant Cell, Vol 10, 813-823 May 1998. The disclosure in the paper does not recognise plants having increased levels of BiP or methods of increasing such protein levels would result in an accelerated response to pathogen attack or infection. Indeed, one of ordinary skill would have concluded that BiP induction may be a consequence of stress occurring from the increased production of defense related proteins. The opposite is shown to occur based on several key findings in the application as filed, including:

1) BiP gene induction occurs prior to the induction of defense-related proteins (Figure 1A) and is unrelated to the unfolded protein response (Figure 4). These findings were published and confirmed in Jelitto-Van Dooren et al., 1999. Plant Cell 11, 1935-1943, a date one year after the priority date of the present patent application and could not be deduced from the Crofts et al., 1998 disclosure.

2) An independent assay based on the plant signalling molecule salicylic acid showing that BiP synthesis occurs much earlier than PR1 synthesis and must therefore be due to a novel mechanism (Figure 7). This finding could not be deduced from Crofts et al., 1998 disclosure.

3) The finding that BiP over expression leads to accelerated induction of defence related proteins, illustrated by the complete induction of PR1 after merely 6 hours in BiP overproducing plants in contrast to 24 hours in wild type plants (Figure 12A), which led to the novel working model (Figure 17) which is the main foundation to the invention.

Such findings are not disclosed in Crofts et al 1998, The Plant Cell, Vol 10, 813-823 May 1998, moreover neither one of ordinary skill in the art of plant biochemistry or plant pathology, nor the authors of Crofts et al., 1998 themselves could have deduced or predicted such unexpected findings.

4. I believe that the present invention is not only fully supported for methods of overexpressing any BiP but that increased levels of BiP conferring a plant with an accelerated response time to pathogen attack is not disclosed in the prior art nor is the effect of BiP predictable.

5. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Jurgen Denecke, PhD.

05/10/2004
Date

Appendix I Overview of BiP sequences in the public domain

AIa. Examples of non-plant BiPs published before filing in December 1998

Saccharomyces cerevisiae (brewers yeast)
Rose MD, Misra LM, Vogel JP.
KAR2, a karyogamy gene, is the yeast homolog of the mammalian BiP/GRP78 gene.
Cell. 1989 Jun 30;57(7):1211-21.

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  1 mffnrlsagk llvplsvvly alfvvilplq nsfhssnvlv
 41 rgaddvenyg tvigidlgtt yscvavmkng kteilaneqg
 81 nritpsyvaf tdderligda aknqvaanpq ntifdikrli
121 glkyndrsvq kdikhlpfnv vnkdgkpave vsvkgekkvf
161 tpeeisgmil gkmkqiaedy lgtkvthavv tvpayfndaq
201 rqatkdagti aglnvlrivn eptaaaiayg ldksdkehqi
241 ivydlgggtf dvsllsieng vfevqatsgd thlggedfdy
281 kivrqlikaf kkkhgidvsd nnkalaklkr eaekakrals
321 sqmstrieid sfvdgidlse tltrakfeel nldlfkktlk
361 pvekvlqdsg lekkdvddiv lvggstripk vqqllesyfd
401 gkkaskginp deavaygaav qagvlsgeeg vedivlldvn
441 altlgiettg gvmtplikrn taiptkksqi fstavdnqpt
481 vmikvyeger amskdnnllg kfeltgippa prgvpqievt
521 faldangilk vsatdkgtgk sesititndk grltqeeidr
561 mveeaekfas edasikakve srnklenyah slknqvngdl
601 gekleeedke tlldaandvl ewlddnfeta iaedfdekfe
641 slskvaypit sklyggadgs gaadyddede dddgdyfehd
681 el
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Aspergillus (filamentous mold)
Hijarrubia, M. J., Casqueiro, J., Gutierrez, S., Fernandez, F. J., and Martin, J. F.
Characterization of the bip gene of Aspergillus awamori encoding a protein with an HDEL retention signal homologous to the mammalian BiP
involved in polypeptide secretion.
Curr Genet 32, 139-46 (1997).

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  1 marishqgaa kpftawttif ylllvfiapl affgtahaqd
 41 etspqesygt vigidlgtty scvgvmqngk veilvndqgn
 81 ritpsyvaft deerlvgdaa knqyaanprr tifdikrlig
121 rkfddkdvqk dakhfpykvv nkdgkphvkv dvnqtpktlt
161 peevsamvlg kmkeiaegyl gkkvthavvt vpayfndaqr
201 qatkdagtia glnvlrvvne ptaaaiaygl dktgderqvi
241 vydlgggtfd vsllsidngv fevlatagdt hlggedfdqr
281 vmdhfvklyn kknnvdvtkd lkamgklkre vekakrtlss
321 qmstrieiea fhngedfset ltrakfeeln mdlfkktlkp
361 veqvlkdakv kksevddivl vggstripkv qalleeffgg
401 kkaskginpd eavafgaavq ggvlsgeegt gdvvlmdvnp
441 ltlgiettgg vmtklipmnt viptrksqif staadnqptv
481 liqvyegers ltkdnnllgk feltgippap rgvpqievsf
521 dldangilkv hasdkgtgka esititndkg rlsqeeidrm
561 vaeaeefaee dkaikakiea rntlenyafs lknqvndeng
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601 lggqideddk qtildavkev tewlednaat attedfeeqk
641 eqlsnvaypi tsklygsapa deddepsghd el

Nematode worm
Wilson,R.
Genome sequence of the nematode C. elegans: a platform for investigating biology. The C. elegans Sequencing Consortium
JOURNAL Science 282 (5396), 2012-2018 (1998)

1 mktlfllgli alsavsvyce eeektekket kygtiigidl gttyscvgvy kngrveiian
61 dqgnritpsy vafsgdqgdr ligdaaknql tinpentifd akrligrdyn dktvqadikh
121 wpfkvidksn kpsvevkvgs dnkqftpeev samvlvkmke iaesylgkev knavvtvpay
181 fndaqrqatk dagtiaglnv vriineptaa aiaygldkkd gernilvfdl gggtfdvsml
241 tidngvfevl atngdthlgg edfdqrvmey fiklykkksg kdlrkdkrav qklrreveka
301 kralstqhqt kveieslfdg edfsetltra kfeelnmdlf ratlkpvqkv ledsdlkkdd
361 vheivlvggs tripkvqqli keffngkeps rginpdeava ygaavqggvi sgeedtgeiv
421 lldvnpltmg ietvggvmtk ligrntvipt kksqvfstaa dnqptvtiqv fegerpmtkd
481 nhqlgkfdlt glppaprgvp qievtfeidv ngilhvtaed kgtgnknkit itndqnrlsp
541 edierminda ekfaeddkkv kdkaearnel esyaynlknq iedkeklggk ldeddkktie
601 eaveeaiswl gsnaeasaee lkeqkkdles kvqpivskly kdagaggeea peegsddkde
661 l

Chicken
Stoeckle,M.Y., Sugano,S., Hampe,A., Vashistha,A., Pellman,D. and Hanafusa,H.
78-kilodalton glucose-regulated protein is induced in Rous sarcoma virus-transformed cells independently of glucose deprivation
Mol. Cell. Biol. 8 (7), 2675-2680 (1988)

1 mrhlllalll lggaraddee kkedvgtvvg idlgttyscv gvfkngrvei iandqgnrit
61 psyvaftpeg erligdaakn qltsnpentv fdakrligrt wndpsvqqdi kylpfkvvek
121 kakphiqvdv gggqtktfap eeisamvltk mketaeaylg kkvthavvtv payfndaqrq
181 atkdagtiag lnvmriinep taaaiaygld kregeknilv fdlgggtfdv slltidngvf
241 evvatngdth lggedfdqrv mehfiklykk ktgkdvrkdn ravqklrrev ekakralssq
301 hqarieiesf fegedfsetl trakfeelnm dlfrstmkpv qkvledsdlk ksdideivlv
361 ggstripkiq qlvkeffngk epsrginpde avaygaavqa gvlsgdqdtg dlvlldvcpl
421 tlgietvggv mtklprntv vptkksqifs tasdnqptvt ikvyegerpl tkdnhllgtf
481 dltgippapr gvpqievtfe idvngilrvt aedkgtgnkn kititndqnr ltpeeiermv
541 ndaekfaeed kklkeridar nelesyaysl knqigdkekl ggklssedke tiekaveeki
601 ewleshqdad iedfkskkke leevvqpivs klygsagppp tgeeeaaekd el

Chinese Hamster
Ting,J., Wooden,S.K., Kriz,R., Kelleher,K., Kaufman,R.J. and Lee,A.S.
The nucleotide sequence encoding the hamster 78-kDa glucose-regulated protein (GRP78) and its conservation between hamster and rat
Gene 55 (1), 147-152 (1987)

1 mkfpmvaaal lllcavraee edkkedvgtv vgidlgttys cvgvfkngrv eiiandqgnr
61 itpsyvaftp egerligdaa knqltsnpen tvfdakrlig rtwndpsvqq dikflpfkvv
121 ekktkpyiqv digggqtktf apeeisamvl tkmketaeay lgkkvthavv tvpayfndaq
181 rqatkdagti aglnvmriin eptaaaiayg ldkregekni lvfdlgggtf dvslltidng
241 vfevvatngd thlggedfdq rvmehfikly kkktgkdvrk dnravqklrr evekakrals
301 sqhqarieie sffegedfse tltrakfeel nmdlfrstmk pvqkvledsd lkksdideiv
361 lvggstripk iqqlvkeffn gkepsrginp deavaygaav qagvlsgdqd tgdlvlldvc
421 pltlgietvg gvmtklipm tvvptkksqi fstasdnqpt vtikvyeger pltkdnhllg
481 tfdltgippa prgvpqievt feidvngilr vtaedkgtgn knkititndq nrltpeeier
541 mvndaekfae edkklkerid trnelesyay slknqigdke klggklssed ketmekavee
601 kiewleshqd adiedfkakk keleeivqpi isklygsagp pptgeedtse kdel

Mouse
Kozutsumi,Y., Normington,K., Press,E., Slaughter,C., Sambrook,J.
and Gething,M.J.
Identification of immunoglobulin heavy chain binding protein as
glucose-regulated protein 78 on the basis of amino acid sequence,
immunological cross-reactivity, and functional activity
J. Cell Sci. Suppl. 11, 115-137 (1989)

1 mmkftvvaaa llllgavrae eedkkedvgt vvgidlgtty scvgvfkngr veiiandqgn
61 ritpsyvaft pegerligda aknqltsnpe ntvfdakrli grtwndpsvq qdikflpfkv
121 vekktkpyiq vdigggqtkt fapeeisamv ltkmketaea ylgkkvthav vtvpayfnda
181 qrqatkdagt iaglnvmrii neptaaaiay gldkregekn ilvfdlgggt fdvslltidn
241 gvfevvatng dthlggedfd qrvmehfikl ykkktgkdvr kdnravqklr revekakral
301 ssqhqariei esffegedfs etltrakfee lnmdlfrstm kpvqkvleds dlkksdidei
361 vlvggstrip kiqqlvkeff ngkepsrgin pdeavaygaa vqagvlsgdq dtgdlvlldv
421 cpltlgietv ggvmtklipr ntvvptkksq ifstasdnqp tvtikvyege rpltkdnhll
481 gtfdltgipp aprgvpqiev tfeidvngil rvtaedkgtg nknkititnd qnrltpeeie
541 rmvndaekfa eedkklkeri dtrnelesya yslknqigdk eklggklsse dketmekave
601 ekiewleshq dadiedfkak kkeleeivqp iisklygsgg ppptgeedts ekdel

AIb. A selection of plant BiP sequences published before filing in December 1998

Cloning of tobacco BiP in 1991 was the first evidence for multigene families for this class of protein in plants, accompanied by functional complementation in the yeast Saccharomyces cerevisiae, which represents a cross-Kingdom complementation and demonstrates extreme functional conservation. Tobacco BiP contains 8 or more isoforms which are over 90% identical. The patent is based on experiments conducted on isoform 4 (BLP4), but the other isoforms are exchangeable. At the time of filing, it was clear to anybody in the field that functional complementation between a plant BiP and yeast BiP demonstrates functional conservation so that any BiP could be used.

Tobacco BiP isoform BLP4 (one of 8 cloned isoforms)
Denecke, J., Souza Goldman, M.H., Demolder, J., Seurinck, J. and Botterman, J. (1991). The tobacco lumenal binding protein is encoded by a multigene family. The Plant Cell **3**, 1025-1035.

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   1 maggawnrrt slivfgivlf gclfafsiat eeatklgtvi gidlgttysc vgvyknghve
  61 iiandqgnri tpswvaftdg erligeaakn laavnpertv fdvkrligrk fddkevqrdm
 121 klvpykivnk dgkpyiqvki kdgetkifsp eeisamiltk mketaeaylg kkikdavvtv
 181 payfndaqrq atkdagviag lnvariinep taaaiaygld kkggeknilv fdlgggtfdv
 241 siltidngvf evlstngdth lggedfdqri meyfiklikk khgkdiskdn ralgklrrea
 301 erakralssq hqvrveiesl fdgvdfsepl trarfeelnn dlfrktmgpv kkamddagle
 361 ktqideivlv ggstripkvq qllkdyfdgk epnkgvnpde avaygaavqg gilsgeggde
 421 tkdillldva pltlgietvg gvmtkliprn tviptkksqv fttyqdqqtt vtiqvfeger
 481 sltkdcrllg kfdltgiapa prgtpqievt fevdangiln vkaedkasgk sekititndk
 541 grlsqeeier mvkeaeefae edkkvkerid arnsletyvy rimrnqindkd kladklesde
 601 kekietatke alewlddnqs aekedyeekl keveavcnpi itavyqksgg apggesgase
 661 dddhdel
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Arabidopsis thaliana (one of three isoforms in this species)
Koizumi, N.
Isolation and responses to stress of a gene that encodes a luminal binding protein in Arabidopsis thaliana
Plant Cell Physiol. 1996
Volume 37
862-865

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   1 marsfganst vvlaiiffgc lfafstakee atklgsvigi dlgttyscvg vyknghveii
  61 andqgnritp swvgftdser ligeaaknqa avnpertvfd vkrligrkfe dkevqkdrkl
 121 vpyqivnkdg kpyiqvkikd getkvfspee isamiltkmk etaeaylgkk ikdavvtvpa
 181 yfndaqrqat kdagviagln variinepta aaiaygldkk ggeknilvfd lgggtfdvsv
 241 ltidngvfev lstngdthlg gedfdhrime yfiklikkkh qkdiskdnka lgklrrecer
 301 akralssqhq vrveieslfd gvdlsepltr arfeelnndl frktmgpvkk amddaglqks
 361 qideivlvgg stripkvqql lkdffegkep nkgvnpdeav aygaavqggi lsgeggdetk
 421 dillldvapl tlgietvggv mtkliprntv iptkksqvft tyqdqqttvs iqvfegersl
 481 tkdcsllgkf dltgvppapr gtpqievtfe vdangilnvk aedkasgkse kititnekgr
 541 lsqeeidrmv keaeefaeed kkvkekidar naletyvynm knqvsdkdkl adklegdeke
 601 kieaatkeal ewldenqnse keeydeklke veavcnpiit avyqrsggap gaggesstee
 661 edeshdel
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Glycine max (Soybean)
Figueiredo,J.E.F., Cascardo,J.M., Carolino,S.M.B., Alvin,F. and Fontes,E.P.B.
Water-stress regulation and molecular analysis of the soybean BIP gene family
Braz. J. Plant Physiol. 9, 103-110 (1997)

1 magswarrsl ivlaiisfgc lfaisiakee atklgtvigi dlgttyscvg vyknghveii
61 annqgnritp swvaftdser ligeaaknla avnpertifd vkrligrkfe dkevqrdmkl
121 vpykivnkdg kpyiqvkikd getkvfspee isamiltkmk etaeaflgkk indavvtvpa
181 yfndaqrqat kdagviagln variinepta aaiaygldkk ggeknilvfd lgggtfdvsi
241 ltidngvfev latngdthlg gedfgqrime yfiklikkkh gkdiskdnra lgklrreaer
301 akralssqhq vrveieslfd gvdfsepltr arfeelnndl frktmgpvkk amedaglqks
361 qideivlvgg stripkvqql lkdyfdgkep nkgvnpdeav aygaavqegi lsgeggeetk
421 dillldvapl tlgietvggv mtklprntv iptkksqvft tyqdqqttvs iqvfegersl
481 tkdcrllgkf dlsgippapr gtaqievtfe vdangilnvk aedkgtgkse kititnekgr
541 lsqeeiermv reekdfaeee kkvkeridar nsletyvynm knqvsdkdkl adklesdeke
601 kietavkeal ewlddnqsme kedyeeklke veavcnpiis avyqrsggap ggggasgeed
661 eddshdel

Rice
Muench,D.G., Wu,Y., Zhang,Y., Li,X., Boston,R.S. and Okita,T.W.
Molecular cloning, expression and subcellular localization of a BiP homolog from rice endosperm tissue
Plant Cell Physiol. 38 (4), 404-412 (1997)

1 mdrvrgsafl lgvllagslf afsvakeetk klgtvigidl gttyscvgvy knghveiian
61 dqgnritpsw vaftdserli geaaknqaav npertifdvk rdigrkfeek evqrdmklvp
121 ykivnkigkp yiqvkikdge nkvfspeevs amilgkmket aeaylgkkin davvtvpayf
181 ndaqrqatkd agviaglnva riineptaaa iaygldkkgg eknilvfdlg ggtfdvsilt
241 idngvfevla tngdthlgge dfdqrimeyf iklikkkysk diskdnralg klrreaerak
301 ralsnqhqvr veieslfdgt dfsepltrar feelnndlfr ktmgpvkkam ddagleksqi
361 heivlvggst ripkvqqllr dyfegkepnk gvnpdeavay gaavqgsils geggdetkdi
421 llldvapltl gietvggvmt klipmtvip tkksqvftty qdqqttvsiq vfegersmtk
481 dcrllgkfdl sgipaaprgt pqievtfevd angilnvkae dkgtgkseki titnekgrls
541 qeeidrmvre aeefaeedkk vkeridarnq letyvynmkn tvgdkdklad kleseekekv
601 eealkealew ldenqtaeke eyeeklkeve avcnpiisav yqrtggapgg rrrgrlddeh
661 del

Maize
Wrobel,R.L., OBrian,G.R. and Boston,R.S.
Comparative analysis of BiP gene expression in maize endosperm
Gene 204 (1-2), 105-113 (1997)

1 mdrvrgsafl lgvllagslf afsvakeetk klgtvigidl gttyscvgvy knghveiian
61 dqgnritpsw vaftdserli geaaknqaav npertifdvk rligrkfqdk evqrdmklvp
121 ykiinkdgkp yiqvkikdge nkvfspeeis amilgkmkdt aeaylgkkin davvtvpayf
181 ndaqrqatkd agviaglnva riineptaaa iaygldkkgg eknilvfdlg ggtfdvsilt
241 idngvfevla tngdthlgge dfdqrimeyf iklikkkysk diskdnralg klrreaerak
301 ralsnqhqvr veieslfdgt dfsepltrar feelnndlfr ktmgpvkkam edagleksqi
361 heivlvggst ripkvqqllk dyfngkepnk gvnpdeavaf gaavqgsils geggdetkdi
421 llldvapltl gietvggvmt klipmtvip tkksqvftty qdqqttvsiq vfegersmtk
481 dcrllgkfdl ngipsaprgt pqievtfevd angilnvkae dkgtgkseki titnekgrls
541 qeeidrmvre aeefaeedkk vkeridarnq letyvynmkn tvgdkdklad kleaeekekv
601 eealkealew lddnqsaeke dyeeklkeve avcnpivsav yqrsggapgg dadggvdddh

661 del

Spinach

Anderson,J.V., Neven,L.G., Li,Q.B., Haskell,D.W. and Guy,C.L.
A cDNA encoding the endoplasmic reticulum-luminal heat-shock protein from spinach (Spinacia oleracea L.)
Plant Physiol. 104 (1), 303-304 (1994)

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   1 mavawksras siafgivllg slfafvsakd eapklgtvig idlgttyscv gvykdgkvei
  61 iandqgnrit pswvaftnde rligeaaknq aaanpertif dvkrligrkf edkevqkdmk
 121 lvpykivnrd gkpyiqvkvq egetkvfspe eisamiltkm ketaetflgk kikdavvtvp
 181 ayfndaqrqa tkdagviagl nvariinept aaaiaygldk rggeknilvf dlgggtfdvs
 241 vltidngvfe vlatngdthl ggedfdqrlm eyfiklikkk htkdiskdnr algklrrece
 301 rakralssqh qvrveieslf dgvdfseplt rarfeelnnd lfrktmgpvk kamddaglek
 361 nqideivlvg gstripkvqq llkeffngke pskgvnpdea vafgaavqgs ilsgeggeet
 421 keillldvap ltlgietvgg vmtkliprnt viptkksqvf ttyqdqqttv tiqvfegers
 481 ltkdcrllgk fdltgiapap rgtpqievtf evdangilnv kaedkasgks ekititndkg
 541 rlsqeeierm vreaeefaee dkkvkekida rnsletyiyn mknqisdadk ladklesdek
 601 ekiegavkea lewlddnqsa ekedydeklk eveavcnpii tavyqrsggp sgesgadsed
 661 seeghdel
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